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Effect of weight change on asthma-related health outcomes in patients with severe or difficult-to-treat asthma[☆]

Tmirah Haselkorn^{a,*}, James E. Fish^b, Bradley E. Chipps^c,
Dave P. Miller^d, Hubert Chen^e, Scott T. Weiss^f

^a EpiMetrix, Inc., 902 Aberdeen Drive, Sunnyvale, CA 94087, USA

^b Genentech, Inc., South San Francisco, CA, USA

^c Capital Allergy & Respiratory Disease Center, Sacramento, CA, USA

^d ICON Clinical Research, San Francisco, CA, USA

^e University of California, San Francisco, CA, USA

^f Channing Laboratory, Harvard Medical School, Boston, MA, USA

Received 16 April 2008; accepted 15 August 2008

Available online 25 September 2008

KEYWORDS

Asthma;
ATAQ;
Body mass index;
MiniAQLQ;
TENOR

Summary

Objective: To evaluate the effects of weight change on asthma control, asthma-related quality of life, number of steroid bursts, and exacerbation of asthma symptoms in a population of adult patients with severe or difficult-to-treat asthma who participated in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study.

Methods: We categorized 2396 TENOR patients ≥ 18 years into three groups (≥ 5 lb loss, stable, ≥ 5 lb gain), based on a ± 5 lb (2.27 kg) difference between baseline and 12-month follow-up weight. We used proportional odds and logistic regression models to evaluate the effect of weight change on Asthma Therapy Assessment Questionnaire (ATAQ) and Asthma Quality of Life Questionnaire (AQLQ) scores, exacerbations, and steroid bursts at the 12-month follow-up.

Results: Asthma patients who gained ≥ 5 lb (2.27 kg) during the 12-month interval between baseline and follow-up reported poorer asthma control (adjusted odds ratio [OR]: 1.22; 95% confidence interval [CI]: 1.01–1.49; $p = 0.04$), worse quality of life (least square means: -0.18 ; 95% CI: -0.30 to -0.06 ; $p = 0.003$), and a greater number of steroid bursts (OR: 1.31; CI: 1.04–1.66; $p = 0.02$) than patients who maintained their baseline weight or lost ≥ 5 lb (2.27 kg).

[☆] The TENOR Study is funded by Genentech, Inc. and Novartis Pharmaceuticals Corp.

* Corresponding author. Tel./fax: +1 408 730 2503.

E-mail address: haselkorn.tmirah@gene.com (T. Haselkorn).

Conclusion: Increased weight is associated with worse asthma-related health outcomes. Strategies to prevent weight gain could help patients achieve better asthma control and improve asthma-related quality of life.

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Introduction

Asthma is a chronic condition affecting millions of individuals worldwide and has a substantial incidence rate that continues to rise.¹ Although patients with severe or difficult-to-treat asthma represent a small portion of asthma patients, they account for much of the morbidity, mortality, and costs associated with the disease.² Symptom control is the goal of asthma treatment; however, current levels of control fall short of international guidelines.³

Body mass index (BMI) is positively correlated with asthma incidence and severity.^{1,4,5} Although a handful of studies have reported the beneficial effects of weight loss on asthma symptoms,^{6–9} none have evaluated the effects of weight change on asthma control. To better characterize the relationship between body weight/BMI and asthma control, and the variables that influence it, we analyzed characteristics of severe or difficult-to-treat asthma patients who participated in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR)² study. Our primary objective was to evaluate the effects of weight change on asthma control, asthma-related quality of life (QoL), number of steroid bursts, and asthma exacerbations.

Materials and methods

We analyzed baseline and 12-month follow-up data of TENOR patients ≥ 18 years. Patients were categorized into three groups (≥ 5 lb loss, stable, or ≥ 5 lb gain), based on a ± 5 lb (2.27 kg) difference between baseline and 12-month follow-up weight. Five pounds was chosen for assessing weight gain/loss because changes of that magnitude were sufficiently common in our cohort to allow for comparisons, but not likely to be visit-to-visit measurement error. In addition, 5 lb was deemed to be a low, yet reasonable and actionable cutpoint that physicians could easily communicate to their patients.

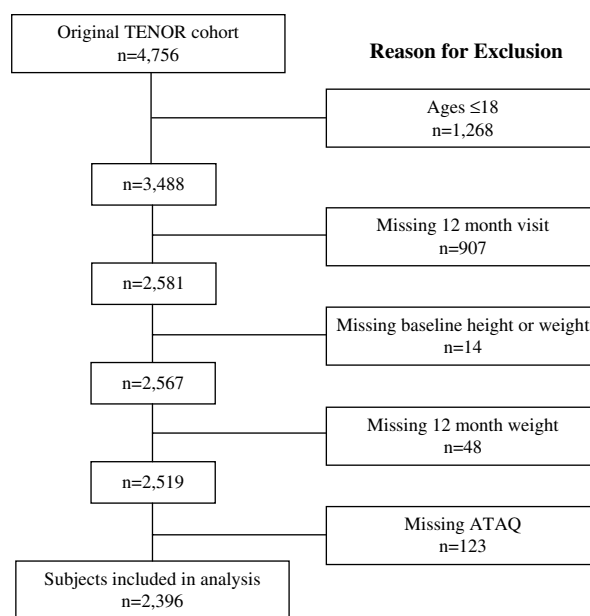
Of the 3488 TENOR patients considered for this analysis, those excluded did not attend a 12-month follow-up visit ($n = 907$), have baseline height and weight ($n = 14$) or 12-month weight ($n = 48$) available, and/or did not complete the Asthma Therapy Assessment Questionnaire (ATAQ)¹⁰ ($n = 123$) (Fig. 1). There were some statistical differences between included and excluded patients; however, those included in the present analysis did not differ from the overall ≥ 18 -year-old cohort with respect to primary analysis variables (e.g. mean age 50 vs. 49 years; baseline BMI 30.4 vs. 30.4; control problems 1.9 vs. 1.8; percent female 72 vs. 71).

Study population

TENOR methodology and baseline population characteristics have been described previously.² Briefly, TENOR was a multicenter, observational study of 4756 patients ≥ 6 years with severe or difficult-to-treat asthma, living in diverse geographical areas of the United States. Patients with mild or moderate asthma were eligible for enrollment if their pulmonologists/allergists considered their asthma difficult-to-treat. At enrollment, patients had been receiving care from their respective asthma specialists for at least 1 year and were frequent users of health care and/or asthma medication. Heavy smokers (≥ 30 pack-years) and patients diagnosed with cystic fibrosis were excluded. There was no experimental intervention, and patients continued to receive medication and treatment prescribed by their asthma specialists. All participants provided written informed consent. The TENOR design and protocol were approved by a central institutional review board and, when necessary, by the institutional review board at each site.

Data collection

Data were collected at baseline and semi-annually via study coordinator-administered interviews. During those visits,



ATAQ = Asthma Therapy Assessment Questionnaire.

Figure 1 Inclusion and exclusion criteria for current analysis.

patients also completed several self-administered questionnaires and reported the previous 3 months' asthma-related health care utilization.

Information about region and mean income were estimated using patients' Zip Code Tabulation Area from the 2000 US Census.¹¹ Geographic location was further classified as "urban" or "rural," according to zip code, as defined in the Rural Urban Commuting Area classification system.¹²

Asthma severity

Pulmonologists/allergists subjectively categorized each patient's asthma as mild, moderate, or severe. Asthma was also categorized according to two classification schemes: the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report-2¹³ and the Global Initiative for Asthma (GINA)¹⁴ guidelines.

Asthma control and asthma-related quality of life

Asthma control was assessed by the ATAQ control index, which ranges from zero to four problems (0 = well-controlled; 1–2 = not well-controlled; 3–4 = poorly controlled). Patients also completed the Mini-Asthma Quality of Life Questionnaire (MiniAQLQ).¹⁵ MiniAQLQ items are scored from one to seven; higher scores represent better QoL. The minimal important difference (MID) for the AQLQ has been estimated to be 0.5.¹⁶

WPAI-asthma

An asthma-specific adaptation of the allergy-specific Work Productivity and Activity Impairment (WPAI-AS)¹⁷ instrument was used to assess work productivity and daily activity (range 0%–100% impairment). The performance characteristics of the WPAI-AS support its validity as a measure of asthma-related impairment in patients with severe or difficult-to-treat asthma.¹⁸

Spirometry

Spirometry was performed according to American Thoracic Society guidelines¹⁹ with a certified device, calibrated daily. Predicted spirometry values were adjusted for race, according to Hankinson reference values.²⁰

Skin test and IgE measurement

Skin test results were self-reported by patients. Total serum IgE concentration (IU/mL) was measured at baseline, using any commercially available assay that met 510 (K) Food and Drug Administration approval and was calibrated to the World Health Organization's Second International Reference Preparation for Human Serum IgE (WHO IRP 75/502).

Statistical analysis

Descriptive analysis

Body weight was compared at baseline and 12-month follow-up for each patient. Patients were categorized into

three groups (≥ 5 lb loss, stable, or ≥ 5 lb gain), based on a ± 5 lb (2.27 kg) change in weight between baseline and follow-up. A core set of variables was summarized for each group. Group comparisons were made using chi-square and *F*-tests for categorical and continuous variables, respectively. Although the analyses were intended for descriptive purposes, we used *p* values to identify potential confounders in our primary analyses.

Primary analyses

We modeled ATAQ at the 12-month follow-up, using a proportional odds model. Weight group was the primary predictor variable and was forced into the model, as were variables that are known to be associated with weight and poor asthma outcomes, including BMI at baseline, age, sex, and race.^{21,22} Additional demographic (i.e. geographic region, urban/rural, education, employment status, income, health care provider) and clinical (i.e. GINA severity, race-adjusted percent predicted forced expiratory volume in 1 s [FEV₁], serum IgE, skin test, history of atopic dermatitis and allergic rhinitis, bronchitis, chronic obstructive pulmonary disease, duration of asthma, oral steroid use, treatment setting) data were included in the model in a stepwise fashion if they were independently predictive of the outcome after considering the variables already included in the model. Unlike the variables that were forced into the model, these potential covariates were only included if they met the entry threshold of $\alpha = 0.05$. For categorical variables with *n* categories, the entry criteria were based on the *n* – 1 degree of freedom test evaluating the statistical significance of the variable as a whole, not the individual categories from which the variable is comprised.

We modeled MiniAQLQ at the 12-month follow-up in a similar way, using a linear regression model. Logistic regression was used to analyze asthma exacerbations (emergency room [ER] visit or hospitalization) and steroid bursts (short-term increase in corticosteroid therapy to treat an exacerbation of symptoms).

Missing data

Patients for whom individual predictor variable information was not available were excluded from the descriptive analyses pertaining to those variables. All analyses were performed with SAS software (v.9.1 or higher; SAS Institute Inc., Cary, NC).

Results

Patient demographics

Of the TENOR patients, 2396 (1730 women, 666 men) met the inclusion criteria. Of those, 652 were classified in the ≥ 5 lb (≥ 2.27 kg) gain group (6–75 lb (2.7–34.1 kg) gained), 557 in the ≥ 5 lb (≥ 2.27 kg) loss group (6–65 lb (2.7–29.5 kg) lost), and 1187 in the stable group (< 5 lb (< 2.27 kg) gained or lost). The groups differed significantly in baseline weight and BMI, age, race, employment status, geographic region, estimated income, and control (Table 1). Among the clinical measures evaluated, mean actual post-

Table 1 Baseline demographics of the 2396 TENOR patients included in the analysis.

Variables	Weight change at 12-month follow-up			p value
	≥5 lb (≥2.27 kg) loss	Stable	≥5 lb (≥2.27 kg) gain	
Total patients, <i>n</i> (%)	557 (23.2)	1187 (49.5)	652 (27.2)	
Mean age, years ± SD	49.7 ± 14.9	51.3 ± 14.7	48.0 ± 13.5	<0.0001
Gender, <i>n</i> (%)				
Female	415 (74.5)	837 (70.5)	478 (73.3)	NS
Male	142 (25.5)	350 (29.5)	174 (26.7)	
Race, <i>n</i> (%)				
White	455 (81.7)	993 (83.7)	523 (80.2)	0.020
Black	71 (12.7)	103 (8.7)	81 (12.4)	
Other	31 (5.6)	91 (7.7)	48 (7.4)	
Education, <i>n</i> (%)				
High school or less	151 (27.1)	337 (28.4)	181 (27.8)	NS
Some college/trade school	197 (34.4)	395 (33.3)	212 (32.5)	
College graduate/advance degree	209 (37.5)	455 (38.3)	259 (39.7)	
Employment status, <i>n</i> (%)				
Full-time	*244 (43.8)	541 (45.6)	337 (51.7)	<0.0001
Part-time	60 (10.8)	164 (13.8)	77 (11.8)	
Student	12 (2.2)	21 (1.8)	17 (2.6)	
Homemaker	50 (9.0)	94 (7.9)	40 (6.1)	
Retired	100 (18.0)	245 (20.6)	84 (12.9)	
Disabled	68 (12.2)	83 (7.0)	71 (10.9)	
Unemployed	23 (4.1)	39 (3.3)	26 (4.0)	
Geographic region, <i>n</i> (%)				
Northeast	*116 (21.0)	*272 (23.1)	*117 (18.1)	0.007
Midwest	112 (20.3)	184 (15.6)	119 (18.4)	
South	148 (26.8)	304 (25.9)	206 (31.8)	
West	176 (31.9)	416 (35.4)	206 (31.8)	
Urban/rural, <i>n</i> (%)				
Urban core	*444 (80.6)	*914 (77.9)	*491 (77.0)	NS
Suburban	47 (8.5)	124 (10.6)	74 (11.6)	
Large town	25 (4.5)	62 (5.3)	35 (5.5)	
Small town/isolated				
Rural	35 (6.4)	74 (6.3)	38 (6.0)	
Mean annual estimated income (USD) ± SD	56,639 ± 20,212	58,813 ± 22,754	55,458 ± 19,500	0.004
Healthcare provider, <i>n</i> (%)				
Commercial/PPO	243 (43.6)	524 (44.1)	285 (43.7)	NS
HMO	138 (24.8)	337 (28.4)	190 (29.1)	
Medicaid	31 (5.6)	46 (3.9)	38 (5.8)	
Medicare	103 (18.5)	212 (17.9)	92 (14.1)	
Other	42 (7.5)	68 (5.7)	47 (7.2)	

*Some patient data missing for these variables. HMO = health maintenance organization; NS = not significant; PPO = preferred provider organization; TENOR = The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; USD = United States dollar.

bronchodilator FEV₁/FVC was statistically different between the three groups ($p < 0.05$); however, the differences were not clinically meaningful (Table 2). Baseline medication use was similar between the groups, except for oral steroid use ($p = 0.048$). The histograms in Fig. 2 show that the distribution of patient weight was similar to that of

BMI at baseline and at 12-month follow-up, and weight change and BMI percent change were normally distributed at 12-month follow-up. Approximately 741 (39%) of the patients fell into the overweight category (i.e. BMI ≥25–<30), and at least 1052 (44%) met the criteria for obesity (i.e. BMI ≥30).²³

Table 2 Baseline clinical characteristics of the 2396 TENOR patients included in the analysis.

Variables	≥5 lb (≥2.27 kg) loss	Stable	≥5 lb (≥2.27 kg) gain	p value
Total patients, n (%)	557 (23.2)	1187 (49.5)	652 (27.2)	
Mean BMI (kg/m ²) ± SD	32.5 ± 8.0	29.4 ± 7.2	30.6 ± 7.3	<0.0001
Mean body weight (lb) ± SD	197.9 ± 51.0	177.2 ± 45.2	186.0 ± 46.3	<0.0001
Mean post-bronchodilator % predicted FEV ₁ ± SD	78.6 ± 22.1	78.0 ± 22.9	80.3 ± 22.4	NS
Mean post-bronchodilator actual FEV ₁ /FVC (%) ± SD	72.7 ± 11.9	70.8 ± 12.2	72.1 ± 11.9	0.007
Mean race-adjusted post-bronchodilator % predicted FEV ₁ ± SD	76.6 ± 20.6	75.6 ± 21.2	77.8 ± 20.8	NS
Treating specialist, n (%)				
Pulmonologist	*161 (29.9)	*310 (26.9)	*156 (24.8)	NS
Allergist	377 (70.1)	842 (73.1)	473 (75.2)	
Physician-assessed severity, n (%)				
Mild	*9 (1.6)	34 (2.9)	16 (2.5)	NS
Moderate	260 (46.8)	561 (47.3)	300 (46.0)	
Severe	287 (51.6)	592 (49.9)	336 (51.5)	
NAEPP severity, n (%)				
Mild	119 (21.5)	294 (25.0)	170 (26.3)	NS
Moderate	155 (28.0)	344 (29.3)	182 (28.1)	
Severe	279 (50.5)	536 (45.7)	295 (45.6)	
GINA severity, n (%)				
Mild	*19 (3.5)	*28 (2.4)	*12 (1.9)	NS
Moderate	205 (37.3)	488 (41.8)	253 (39.2)	
Severe	325 (59.2)	652 (55.8)	381 (59.0)	
Oral steroid use, n (%)	135 (24.3)	237 (20.0)	123 (18.9)	0.048
ATAQ control problems, n (%)				
0	89 (16.3)	222 (19.0)	101 (15.7)	0.003
1	103 (18.9)	256 (21.9)	115 (17.8)	
2	162 (29.7)	377 (32.2)	208 (32.2)	
3+	192 (35.2)	315 (26.9)	221 (34.3)	
Skin test result, n (%)				
Positive	*445 (81.1)	*970 (82.0)	*542 (83.5)	NS
Negative	32 (5.8)	65 (5.5)	34 (5.2)	
Never tested	72 (13.1)	148 (12.5)	73 (11.2)	
COPD, n (%)				
Yes	50 (9.0)	108 (9.1)	42 (6.4)	NS
No	507 (91.0)	1079 (90.9)	610 (93.6)	
Bronchitis, n (%)				
Yes	209 (37.5)	428 (36.1)	*225 (34.6)	NS
No	348 (62.5)	759 (63.9)	426 (65.4)	
History of allergic rhinitis, n (%)				
Yes	398 (71.5)	848 (71.4)	481 (73.8)	NS
No	41 (7.4)	87 (7.3)	39 (6.0)	
Not sure	118 (21.2)	252 (21.2)	132 (20.2)	
History of atopic dermatitis, n (%)				
Yes	68 (12.2)	167 (14.1)	*92 (14.1)	NS
No	360 (64.6)	781 (65.8)	433 (66.5)	
Not sure	129 (23.2)	239 (20.1)	126 (19.4)	

(continued on next page)

Table 2 (continued)

Variables	≥5 lb (≥2.27 kg) loss	Stable	≥5 lb (≥2.27 kg) gain	p value
IgE IU/mL				
Geometric mean	81.6	87.2	76.7	NS
95% CI	80.0–93.9	79.1–96.0	67.8–86.8	
Median	94.5	89.0	78.0	
Range	1–6,859	1–15,101	1–5,128	

*Some patient data missing for these variables. ATAQ = Asthma Therapy Assessment Questionnaire; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; GINA = Global Initiative for Asthma; NAEPP = National Asthma Education and Prevention Program; NS = not significant.

Outcome measures

At the 12-month follow-up, the groups differed on ATAQ, MiniAQLQ, and WPAI-AS scores; mean post-bronchodilator FEV₁/FVC; and steroid bursts and ER visits (Table 3). The ≥5 lb (≥2.27 kg) gain group had the highest impairment scores and the lowest QoL scores, and they reported the greatest number of control problems and steroid bursts. The ≥5 lb (≥2.27 kg) loss group reported the greatest number of ER visits.

Asthma control

Patients who gained ≥5 lb (≥2.27 kg) between baseline and follow-up reported poorer asthma control than patients who maintained their baseline weight or lost ≥5 lb (≥2.27 kg) (unadjusted odds ratio [OR]: 1.36; 95% confidence interval [CI]: 1.14–1.61; $p = 0.0005$). The association was maintained when baseline BMI, age, gender, race, treatment specialist, oral steroid use, employment status, presence of bronchitis, history of allergic rhinitis, and GINA asthma severity were included in the model (adjusted OR: 1.22; 95% CI: 1.01–1.49; $p = 0.04$) (Fig. 3). Baseline BMI

and age; being female; being black rather than white; and being disabled rather than employed full-time were independently associated with poor control (all $p < 0.05$). Poor control was also independently associated with being treated by a pulmonologist rather than an allergist; having a GINA assessment of severe, rather than mild, asthma; having a history of allergic rhinitis; having bronchitis; and using oral steroids (all $p < 0.05$).

Quality of life

Weight gain and loss were associated with asthma-related QoL, as assessed with the MiniAQLQ (least square [LS] means: -0.24 ; 95% CI: -0.36 to -0.11 ; $p = 0.0003$; and LS means: -0.14 ; 95% CI: -0.28 – 0.01 ; $p = 0.03$, respectively). However, after adjusting for baseline BMI and age, gender, race, education, estimated income, employment status, health care provider, oral steroid use, bronchitis, atopic dermatitis, treatment specialist, and asthma severity, only weight gain was associated with asthma-related QoL (LS means: -0.18 ; 95% CI: -0.30 to 0.06 ; $p = 0.003$) (Fig. 3).

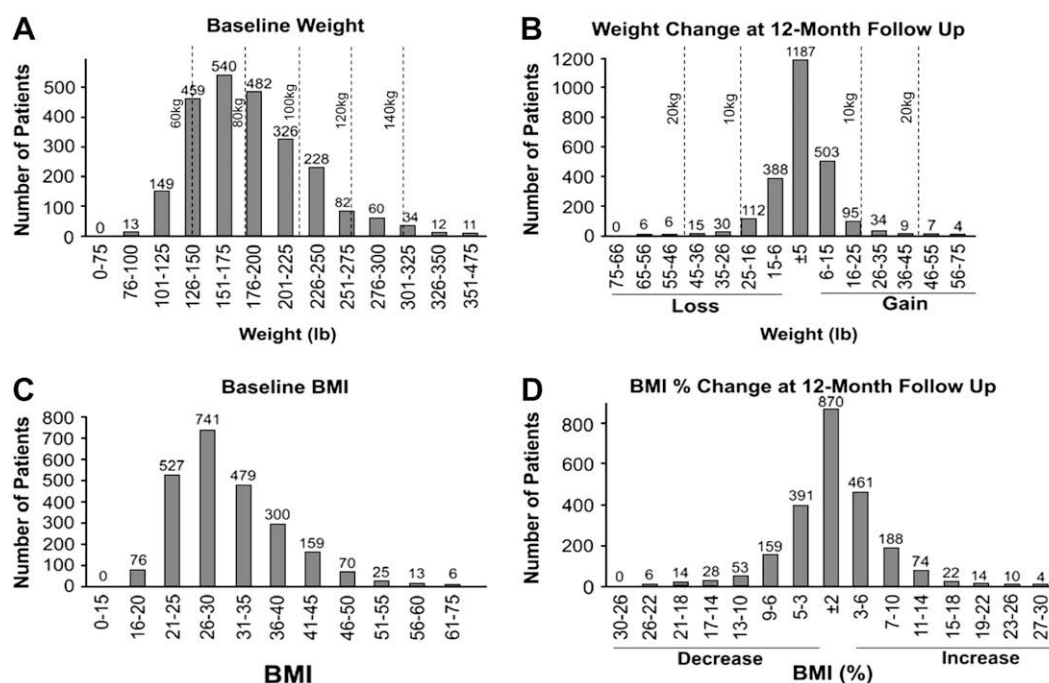


Figure 2 Baseline measures of patient body weight (A) and BMI (C) and changes in body weight (B) and BMI (D) at the 12-month follow-up. BMI = body mass index.

Table 3 Outcome measures at 12-month follow-up.

Variables	Weight change at 12-month follow-up			<i>p</i> value
	≥5 lb (≥2.27 kg) loss	Stable	≥5 lb (≥2.27 kg) gain	
Total patients, <i>n</i> (%)	557 (23.2)	1187 (49.5)	652 (27.2)	
Mean post-bronchodilator % predicted FEV ₁ ± SD	80.2 ± 21.7	78.7 ± 22.1	79.1 ± 22.9	NS
Mean post-bronchodilator actual FEV ₁ /FVC (%) ± SD	72.8 ± 12.0	71.2 ± 12.3	72.1 ± 11.8	0.046
Mean race-adjusted % predicted FEV ₁ ± SD	78.7 ± 21.3	76.2 ± 20.3	76.7 ± 20.9	NS
Overall MiniAQLQ score, mean ± SD	5.0 ± 1.4	5.1 ± 1.3	4.9 ± 1.4	0.001
ATAQ control problems, <i>n</i> (%)				
0	180 (32.3)	399 (33.6)	193 (29.6)	0.009
1	125 (22.4)	295 (24.9)	134 (20.6)	
2	146 (26.2)	304 (25.6)	176 (27.0)	
3+	106 (19.0)	189 (15.9)	149 (22.9)	
WPAI-Asthma % overall work impairment, mean ± SD	16.9 ± 23.7	13.1 ± 20.6	19.4 ± 27.2	<0.0001
WPAI-Asthma % overall activity impairment, mean ± SD	26.1 ± 27.6	23.8 ± 26.7	29.0 ± 28.6	0.001
Overnight hospitalization in previous 3 months, <i>n</i> (%)				
Yes	*18 (3.2)	*31 (2.6)	*19 (2.9)	NS
No	538 (96.8)	1150 (97.4)	631 (97.1)	
ER visit in previous 3 months, <i>n</i> (%)				
Yes	*62 (11.2)	*73 (6.2)	*56 (8.6)	0.001
No	494 (88.8)	1108 (93.8)	594 (91.4)	
Unscheduled office visit in previous 3 months, <i>n</i> (%)				
Yes	*156 (28.1)	*326 (27.6)	*205 (31.5)	NS
No	400 (71.9)	855 (72.4)	445 (68.5)	
Steroid burst in previous 3 months, <i>n</i> (%)				
Yes	*173 (31.2)	*354 (30.0)	*234 (36.3)	0.020
No	382 (68.8)	827 (70.0)	411 (63.7)	

*Some patient data missing. ATAQ = Asthma Therapy Assessment Questionnaire; ER = emergency room; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; MiniAQLQ = Mini-Asthma Quality of Life Questionnaire; NS = not significant; WPAI-Asthma = Asthma-Specific Work Productivity and Activity Impairment.

Exacerbations

Weight gain and loss were associated with exacerbations (unadjusted OR: 1.52; 95% CI: 1.07–2.15; *p* = 0.02; OR: 1.87; CI: 1.32–2.65; *p* = 0.0004). However, when adjusted for baseline BMI, age, gender, race, health care provider, bronchitis, oral steroid use, and race-adjusted percent predicted FEV₁, associations were not maintained (Fig. 3). Age at baseline; being female; being black rather than white; using oral steroids; using Medicaid or Medicare rather than a preferred provider organization; having bronchitis; and race-adjusted percent predicted FEV₁ were independently associated with exacerbations (all *p* < 0.05).

Steroid bursts

Patients in the ≥5 lb (≥2.27 kg) gain group were more likely to have experienced steroid bursts during the 3 months prior to follow-up (OR: 1.33; CI: 1.09–1.63; *p* = 0.006). That relationship was maintained when adjusted for

baseline BMI and age, gender, race, a history of allergic rhinitis, oral steroid use, skin test, treating specialist, asthma severity assessed by GINA, and race-adjusted percent predicted FEV₁ (OR: 1.31; CI: 1.04–1.66; *p* = 0.02) (Fig. 3). Age at baseline; using oral steroids at baseline; having had a negative skin test vs. not having had a skin test; being treated by a pulmonologist rather than an allergist; and race-adjusted percent predicted FEV₁ were independently associated with steroid bursts (*p* < 0.05).

Discussion

Patients with severe or difficult-to-treat asthma who gained ≥5 lb (≥2.27 kg) between baseline and follow-up reported poorer asthma control, worse QoL, and a greater number of steroid bursts than patients who maintained their baseline weight or lost ≥5 lb (≥2.27 kg). Although the magnitude of differences between groups tended to be small, the findings are consistent with reports that increases in BMI are associated with decreased asthma control and asthma-related QoL.^{24–26}

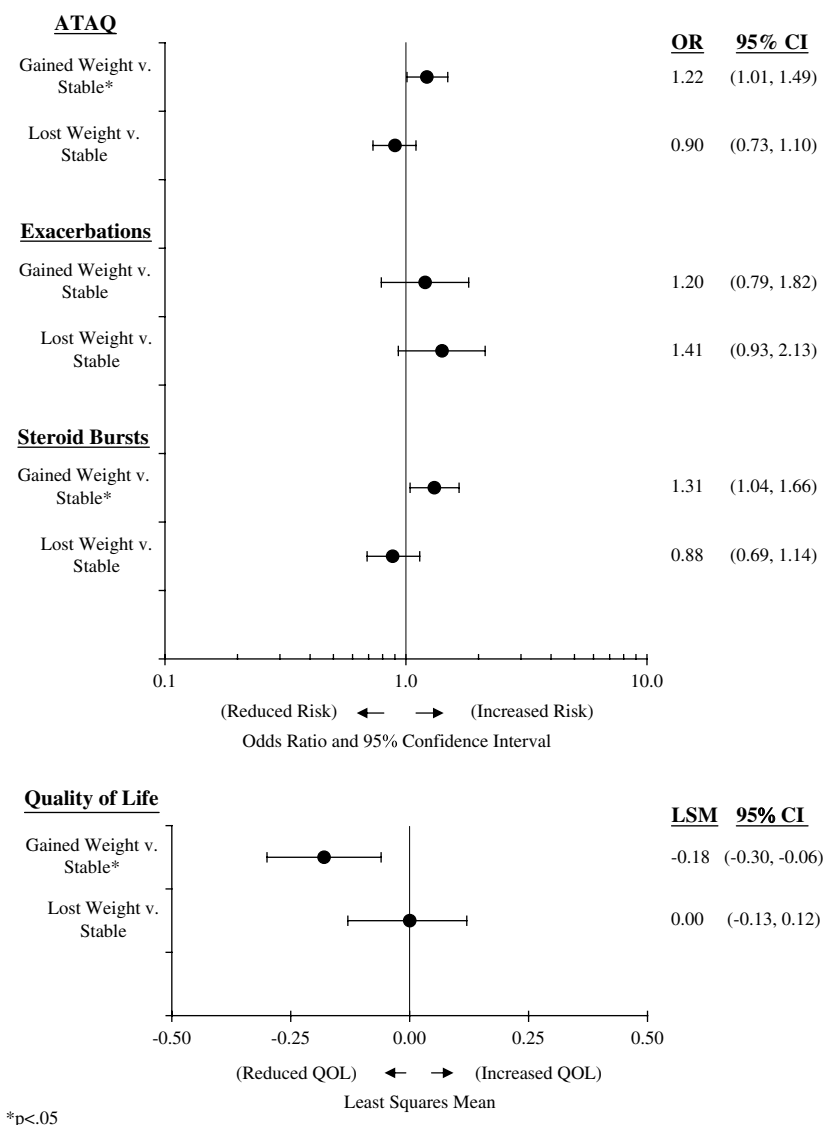


Figure 3 Multivariable regression results assessing the risk of poor asthma control, exacerbations, steroid bursts, and overall quality of life in patients who gained ≥ 5 lb (≥ 2.27 kg) vs. those whose weight remained stable, and in patients who lost ≥ 5 lb (≥ 2.27 kg) vs. those whose weight remained stable.

The association between BMI and asthma is widely recognized (for references and review see Chinn⁴ and Ford¹). However, in many studies it is not clear if increased BMI precedes asthma onset or if it results from physical and physiological restrictions imposed by asthma. In the present study, changes in body weight/BMI preceded ATAQ and MiniAQLQ evaluations. The finding that patients who gained ≥ 5 lb (≥ 2.27 kg) had a greater number of control problems, lower QoL, and more steroid bursts at follow-up suggests that weight gain affected those outcomes rather than vice versa.^{27–30} Although a 5 lb (≥ 2.27 kg) weight change resulted in a 0.23 change in the AQLQ and did not constitute a meaningful difference, if we assume linearity and an MID of 0.5, an 11 lb (5 kg) weight change would correspond to a meaningful change in QoL.

Gender differences in weight gain and asthma control were not specifically evaluated. The literature pertaining to gender differences in the BMI-asthma relationship is

inconsistent; some studies report no gender differences.^{30,31} Others suggest that the relationship is stronger in women^{29,32,33} or that in men asthma is associated with both high and low BMI³⁴ or based on an interaction of gender and race.³⁵ In our study, the relationship between weight gain and poor asthma control was maintained when the model was adjusted for gender, indicating that gender did not modify the BMI-control relationship. One possible reason that gender effects were not apparent in our study is that our analysis was limited to patients with severe or difficult-to-treat asthma. Weight gain may have a greater effect on men with severe or difficult-to-treat asthma than on men with mild or moderate asthma.

Patients who gained ≥ 5 lb (≥ 2.27 kg) reported a greater number of steroid bursts than those who lost or maintained their weight. Weight gain is an often-reported side effect of oral corticosteroids. However, in a previous study of $\approx 18,000$ asthma patients, oral corticosteroid use did not

contribute to obesity.³⁶ In the present study, percent corticosteroid use at baseline was, in fact, lower in patients who gained ≥ 5 lb (≥ 2.27 kg) compared to those who lost weight or remained stable. Despite reporting lower corticosteroid use at baseline, patients who gained ≥ 5 lb (≥ 2.27 kg) had a greater number of steroid bursts at 12-month follow-up. Such data suggest that weight gain may predispose patients to being more symptomatic or increase the severity of existing symptoms, thereby necessitating steroid bursts.

To date, relatively few studies have examined weight loss in relation to asthma outcomes³⁷ and the majority have involved interventions. In these studies, such as the Stenius-Aarniala et al. study³⁸ which included a supervised weight reduction program over an 8 week period, improvements in at least one asthma-related health outcome were observed. Our study did not identify improved outcomes with weight loss. However, TENOR, by design, was a naturalistic study conducted over a 3-year period. Thus, weight gain and loss was random and at the discretion (purposeful or not) of the patient. In addition, mean weight loss in randomized controlled trials, such as the Stenius-Aarniala et al. study (14.2 kg), was much higher than in the TENOR study.

As stated earlier, the 5 lb (2.27 kg) cutpoint was chosen for assessing weight gain/loss because changes of that magnitude were sufficiently common in our cohort to allow for comparisons, but not likely to be visit-to-visit measurement error. In fact, we conducted an analysis using the original 5 lb cutoff, in addition to other thresholds, including 10 lb (4.5 kg), 15 lb (6.8 kg), and 1 standard deviation of the weight difference (11.6 lbs (5.3 kg)). We found that the estimated odds ratios for the ATAQ, exacerbation, and steroid burst outcomes and the least square means for the quality of life outcomes were similar, regardless of the threshold used. However, we lost a fair amount of statistical power at the higher thresholds because confidence bounds became wider due to the stricter definition of weight gain (fewer patients lose greater amounts of weight). This is one of the reasons why we chose the 5 lb cutoff; it was the largest weight cutoff we could use while making estimates of the effects with reasonable precision. In addition, 5 lb was deemed to be a low, yet reasonable and actionable cutpoint that physicians could easily communicate to their patients.

This study had several limitations. First, due to the unrandomized nature of the study, we cannot be certain of a direct causal relationship between weight gain and poor asthma outcomes. Second, asthma control differed between weight groups at baseline. To account for these differences and the possible influence of asthma control on steroid use, a sensitivity analysis in which baseline control was added did not substantially change the results. Third, the outcome measures were based on self-assessments and reports, which were influenced by patients' memory and other psychosocial factors. There is evidence that obese asthma patients tend to rate their symptoms more severely than non-obese patients, although both groups experience similar exacerbations.³⁹ Finally, no measures of body weight distribution or comorbidities associated with weight, such as sleep apnea, were collected in TENOR and thus could not be examined in relation to our findings.

It is clear from our results and those of others^{28,30,40} that the relationship between BMI and asthma is complex, and

interactions of many demographic and clinical variables determine asthma control. Hence, the goal of future studies should be to more closely examine variables that contribute to poor asthma control and determine the threshold at which BMI affects the severity and control of asthma and/or interacts with other variables to affect asthma severity and control.

In conclusion, strategies to prevent weight gain could help patients achieve better asthma control and improve asthma-related QoL. A clearer understanding of the mechanisms by which body weight/BMI influences asthma control and other asthma-related outcomes will enable treatment specialists to formulate treatment programs that include a weight-management component.

Conflict of interest statement

Dr Haselkorn has been a paid consultant to Genentech, Inc. since December 2002. Dr Fish works for and owns stock in Genentech, Inc. Dr Chipps is a paid consultant to and speaker for Genentech, Inc. and receives research funding from Genentech, Inc. Mr Miller is employed by ICON Clinical Research, which receives research funding from Genentech, Inc. and other biotechnology and pharmaceutical companies. Dr Chen is a paid consultant of EpiMetrix, Inc., which receives funding from Genentech, Inc. Dr Weiss has been a paid consultant to Genentech, Inc. since 2001.

Acknowledgment

Writing assistance for this manuscript was provided by Genentech, Inc.

References

1. Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005;115:897–909 [quiz 910].
2. Dolan CM, Fraher KE, Bleecker ER, et al. Design and baseline characteristics of The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2004;92:32–9.
3. Rabe KF, Adachi M, Lai CK, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;114:40–7.
4. Chinn S. Obesity and asthma: evidence for and against a causal relation. *J Asthma* 2003;40:1–16.
5. Burgess JA, Walters EH, Byrnes GB, et al. Childhood adiposity predicts adult-onset current asthma in females: a 25-yr prospective study. *Eur Respir J* 2007;29:668–75.
6. Dixon JB, Chapman L, O'Brien P. Marked improvement in asthma after Lap-Band surgery for morbid obesity. *Obes Surg* 1999;9:385–9.
7. Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. *Chest* 2000;118:1315–21.
8. Macgregor AM, Greenberg RA. Effect of surgically induced weight loss on asthma in the morbidly obese. *Obes Surg* 1993;3:15–21.

9. Stenius-Aarniala B, Poussa T, Kvarnstrom J, et al. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000;**320**:827–32.
10. Vollmer WM, Markson LE, O'Connor E, et al. Association of asthma control with healthcare utilization and quality of life. *Am J Respir Crit Care Med* 1999;**160**:1647–52.
11. US Census Bureau. Census 2000 Summary File. http://factfinder.census.gov/servlet/DCGeoSelectServlet?ds_name=DEC_2000_SF1_U&_ts=171311152142. Accessed January 31, 2008.
12. US Department of Agriculture. 2000 Rural-Urban Commuting Area Codes. <http://www.ers.usda.gov/Briefing/Rural/Data/desc.htm>. Accessed January 31, 2008.
13. National Asthma Education and Prevention Program, National Heart, Lung and Blood Institute, and National Institute of Health Guidelines for the Diagnosis and Management of Asthma. AsthmaExpert Panel Report 2. Bethesda: National Institutes of Health; 1997. NIH 1:97-4051.
14. Global Initiative for Asthma (GINA). A Pocket Guide for Physicians and Nurses. Updated 2004. <http://www.ginasthma.com>. Accessed January 31, 2008.
15. Juniper EF, Guyatt GH, Cox FM, et al. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;**14**:32–8.
16. Juniper EF, Guyatt GH, Willan A, et al. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;**47**:81–7.
17. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;**4**:353–65.
18. Chen H, Blanc PD, Hayden ML, Bleeckers AR, Chawla A, for the TENOR study group. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. *Value Health* 2008;**11**:231–9.
19. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;**152**:1107–36.
20. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med* 1999;**159**:179–87.
21. Chinn S, Downs SH, Anto JM, et al. Incidence of asthma and net change in symptoms in relation to changes in obesity. *Eur Respir J* 2006;**28**:763–71.
22. Skobeloff EM, Spivey WH, St Clair SS, et al. The influence of age and sex on asthma admissions. *JAMA* 1992;**268**:3437–40.
23. National Institutes of Health. NHLBI: Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults: the evidence report. Bethesda: National Institutes of Health; 1998. p. 98–4083.
24. Leynaert B, Neukirch C, Liard R, et al. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. *Am J Respir Crit Care Med* 2000;**162**:1391–6.
25. Lavoie KL, Bacon SL, Labrecque M, et al. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med* 2006;**100**:648–57.
26. Saint-Pierre P, Bourdin A, Chanez P, et al. Are overweight asthmatics more difficult to control? *Allergy* 2006;**61**:79–84.
27. Camargo Jr CA, Weiss ST, Zhang S, et al. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;**159**:2582–8.
28. Young SY, Gunzenhauser JD, Malone KE, et al. Body mass index and asthma in the military population of the northwestern United States. *Arch Intern Med* 2001;**161**:1605–11.
29. Guerra S, Sherrill DL, Bobadilla A, et al. The relation of body mass index to asthma, chronic bronchitis, and emphysema. *Chest* 2002;**122**:1256–63.
30. Huovinen E, Kaprio J, Koskenvuo M. Factors associated to lifestyle and risk of adult onset asthma. *Respir Med* 2003;**97**:273–80.
31. Xu B, Pekkanen J, Laitinen J, et al. Body build from birth to adulthood and risk of asthma. *Eur J Public Health* 2002;**12**:166–70.
32. Beckett WS, Jacobs Jr DR, Yu X, et al. Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Respir Crit Care Med* 2001;**164**:2045–50.
33. Kim S, Camargo Jr CA. Sex-race differences in the relationship between obesity and asthma: the behavioral risk factor surveillance system. *Ann Epidemiol* 2000;**2003**(13):666–73.
34. Luder E, Ehrlich RI, Lou WY, et al. Body mass index and the risk of asthma in adults. *Respir Med* 2004;**98**:29–37.
35. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;**175**:661–6.
36. Hedberg A, Rossner S. Body weight characteristics of subjects on asthma medication. *Int J Obes Relat Metab Disord* 2000;**24**:1217–25.
37. Eneli IU, Skybo T, Camargo Jr CA. Weight loss and asthma: a systematic review. *Thorax* 2008;**63**:671–6.
38. Stenius-Aarniala B, Poussa T, Kvarnström J, Grönlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000;**320**(7238):827–32.
39. Thomson CC, Clark S, Camargo Jr CA. Body mass index and asthma severity among adults presenting to the emergency department. *Chest* 2003;**124**:795–802.
40. Ford ES, Mannino DM, Redd SC, et al. Determinants of quality of life among people with asthma: findings from the Behavioral Risk Factor Surveillance System. *J Asthma* 2004;**41**:327–36.